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An Implantable, Remotely-Programmable Insulin Infusion System

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Abstract

An implantable, remotely-programmable insulin infusion system is described which has a mass of 280 grams and an implanted lifetime exceeding two years. The system uses a rotary solenoid-driven peristaltic pump controlled by low power CMOS timing circuitry which provides bimodal insulin delivery. Fifteen low rates from 0.39 to 5.9 units/hour and 15 high doses from 0.84 to 12.5 units are available using U100 insulin. The system has been tested in the laboratory, evaluated in diabetic dogs, and implanted in one diabetic human.

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AN IMPLANTABLE, REMOTELY-PROGRAMMABLE INSULIN INFUSION SYSTEM

I. Introduction

A variety of "glucose-controlled" and "programmable" insulin infusion systems have been developed in the past few years for diabetes research. The glucose-controlled systems have been reviewed by Albisser.[1] The simpler programmable systems, which employ a bimodal insulin delivery algorithm to control blood glucose, have been reviewed by Spencer.[2] Most programmable systems have been developed for external use, but implantable systems have been reported by Shumakov,[3] Thomas,[4] Perkins,[5] and Prestele.[6] We previously reported the development of a prototype implantable system based on a peristaltic pump driven by a rotary solenoid.[7] In this paper, we describe a more advanced version of that system. Infusion rate is controlled by digital logic and the implantable system is programmed remotely using a hand-held programmer/interrogator unit. This system is bimodal with a continuous basal (low) rate augmented at meal times by a prandial (high) dose. The high dose is initiated by programmed control, and terminated by an automatic return to the low rate at the appropriate time.

II. System Components

The principal components of the implantable system (shown in exploded view in Figure 1) are a titanium enclosure (left half), rate control electronics, batteries, energy storage capacitor and communication coil, a peristaltic pump mounted on a titanium header plate, titanium enclosure (right half), an insulin reservoir and a delivery catheter. In Figure 2, the system is shown assembled with the implantable insulin reservoir and catheter attached. On the right is the hand-held programmer used to communicate rate changes and to request implant status data. The mass of the implant module, exclusive of catheter, insulin reservoir, and protective

Silastic coating, is approximately 280 g (10 oz.). The enclosure dimensions are 75 x 80 x 25 mm (about 3 x 3¼ x 1 inch).

Rotary Solenoid Pump. Insulin delivery systems require low-flow rates (10-20 microliters/hour) for infusion of U100 insulin. A pump has been developed which is capable of accurate low-and high-flow rates, and which has relatively small size, low mass and low power requirements. The pump uses a rotary solenoid to drive a three-roller peristaltic pump head. A prototype version of the pump has previously been described.[8] For the present implant application, both the rotary solenoid prime mover and the peristaltic pump head were modified for reduced mass but no functional design changes were made. The modified pump, shown in Figure 3, weighs 130 g. The pump is 50 mm length by 25 mm diameter (about 2 inch length by 1 inch diameter) and uses 1.5 mm ID by 3.0 mm OD (0.062 by 0.125 inch) silicone rubber tubing. The electromagnetic components of the pump are fabricated from Hyperco-50, an iron-cobalt alloy, while other components are primarily stainless steel.

The prime mover is a type of stepper motor which delivers discrete rotational motions of uniform magnitude with a solenoid-driven ratchet and pawl arrangement. The electromagnetic action of a rotary solenoid is similar to that of a variable reluctance stepper motor. However, for the same volume, the rotary solenoid can generate more torque than stepper motors because every pole on the solenoid rotor is attracted to its corresponding stator pole, whereas conventional stepper motors have only half or less of the poles active during any pulse. Figure 4 shows the present rotary solenoid schematically. A 9-ohm solenoid coil (700 turns of #28 copper wire) is energized by a 31 millisecond square wave pulse from a 7.3 volt source. The solenoid rotor plus drive link and pawl are fastened to a common shaft. Each time the solenoid is energized, the rotor poles are electromagnetically drawn into alignment with the stator poles. As a result, the drive link and pawl rotates the engaged ratchet gear and output

drive shaft one tooth width, clockwise. When the solenoid is deenergized, the drive link is pulled back in the opposite direction by the return spring. The drive pawl is thus indexed for the next pulse by camming over the succeeding tooth of the ratchet gear (which is kept from rotating in the opposite direction by the non-reverse pawl). Accordingly, the peristaltic pump head is driven unidirectionally via the output drive shaft. With each solenoid actuation the pump head is rotated a small fixed angle (10 degrees) equivalent to one tooth of the ratchet gear, and about 2 microliters of fluid are advanced through the elastomeric pump tube.

Small peristaltic pumps often use a single-roller pump head which provides excellent delivery volume accuracy and reproducibility when averaged over several cycles.[9] However, single-roller pumps may show large variations in flow rate during a single rotation of the pump head. Measurements given in the results section showed these flow-rate variations to be unacceptable for our application.

To provide the flow uniformity required for our low flow-rate application a three-roller peristaltic head was developed. By a suitable design of the outer surface of the pump head near the tubing exit, it was possible to minimize pulse-to-pulse variations and to prevent the reverse flow sometimes seen with single-roller pumps. The exit design provides a gradual decompression of the pump tubing over 120 degrees, from fully sealed to fully open. With the three-roller head, at least one roller totally occludes the tubing at all times, preventing fluid leakage. The rotary solenoid pump requires no valves and, since no fluid can flow through the peristaltic head with power loss or most electronic control failures, represents an important system fail-safe feature.

Implant Electronic Control and External Programmer. The implanted electronic control stores rates and other delivery data, controls pump operation, and provides two-way communication with the external programmer.

In addition, it provides data on the implant battery voltage and consistency of pump operations. The design of the control was based on 4000 series CMOS (Complementary Metal Oxide Semiconductor) integrated circuits, analog, bipolar, and discrete components available in chip form from several manufacturers. The design was structured with an emphasis on low component count, high reliability and low power consumption. The assembly was fabricated by RCA, Moorestown, NJ, using thick film hybrid microcircuit technology. Twenty-six CMOS components enclosed in eight leadless hermetic packages were used with timing controlled by a 32 kHz watch crystal. The packages and other components were mounted on both sides of an aluminum oxide substrate. The assembly was conformally coated with parylene for handling and moisture protection. One face of an assembled implant control is shown in Figure 5.

The hand-held external programmer was designed using a CMOS RCA 1802D microprocessor system which supports low-power CMOS integrated circuits, analog and bipolar devices (transmitter, receiver and low programmer battery detector). The RCA microprocessor memory includes 1024 bytes of ultraviolet-erasable, programmable, read-only memory and 128 bytes of CMOS volatile memory. Construction of the programmer includes dual-inline-pack integrated circuits mounted on four-layer printed circuit boards. The entire unit is contained within a modified commercially available plastic housing measuring 45 x 65 x 110 mm (about 1-3/4 x 2½ x 4¼ inches). Power is provided by two AA-size lithium-thionyl chloride cells in series (7.3 V open circuit). An "off-on" switch provides power conservation between uses.

The human input to the programmer is through a four-button keyboard and the output is read from a liquid crystal display with four digits and six annunciators. The human interface was designed to minimize the number of choices a user must make in operating the programmer. Rather than a calculator-like keyboard, the programmer is structured with a "roll and

select" menu which guides the user through the available command functions and program data options. The four input buttons permit 1) selection of the desired command function; 2) entry of function or program data into a storage register; 3) selection of program data (low rate and high dose); and 4) transmission of the chosen command function to the implant. The four output digits define the programmer function number (e.g. 1 = Status Check), the digital input or output data, and various status data. The six annunciators define the displayed digital data (the programmed low rate or high dose, the cumulative dose, or the high dose remaining to be delivered); the delivery mode in effect (low rate or high dose); and the condition of the programmer batteries. Rate and dose data are expressed in units/hour and units of insulin respectively, converted in the programmer software from pump pulse count data. Status data displayed includes complete or incomplete data transmission, battery and flow diagnostics, parity error, rate and dose errors, and operating state (high vs low) error.

Two-way communication between the implant and the hand-held programmer is achieved using induction coupling with a 30 kHz carrier frequency. Communication from the implant to the programmer following Status Check and Beeper On commands (see below) employs mark-space damped data pulses for power conservation. A pulse width modulated data format at a 10 ms rate is used for communication from the programmer to the implant. The communication includes a unique identifying pattern of 8 bits to minimize noise susceptibility followed by four bits which initiate any one of the six functional commands in the implant system, as follows (See Block Diagram, Figure 6):

1. Status Check - Commands the implant to transmit to the programmer 31 bits from the Status Register, consisting of the data parity, a battery voltage check, a flow error check, present delivery mode (low rate or high dose), the programmed rate and dose, the

cumulative dose since the last Reset command, and the high dose remaining to be delivered.

2. Beeper On - Commands the implant to transmit to the programmer a signal coincident with each pump output pulse. The signal is converted to an audible output in the programmer and can be used in lieu of a stethoscope to monitor the implanted system. This feature is also useful in long-term laboratory testing of the system. Any succeeding command cancels the "Beeper On" command.

3. Reset/Stop - This command resets the Dose Counter and clears a flow error, if present. It also interrupts the operation of the implant by stopping the Program Counter. Any succeeding command will restart normal system operation. In the absence of a Reset command, the Dose Counter cycles to zero after 4,096 pulses.

4. Start Low - Commands the implant to return to the low rate delivery mode (sets High/Low latch to "Low").

5. Start High - Commands the implant to begin the high dose delivery mode (sets High/Low latch to "High", and starts the High Dose counter).

6. Reprogram - Commands the implant to accept new program data (rate and dose) through a Data Gate which allows 12 bits of program data into the Program Register. A parity check is made on the incoming data. A parity error interrupts implant operation by stopping the Program Counter. Normal operation is resumed following a successful Reprogram command.

With the six commands described above, considerable flexibility can be used in programming the implant. An instruction from the programmer may actually consist of several commands in sequence. Further, different programmers may be structured to issue different command sequences. For

example, a "Doctor" programmer has been prepared which gives a full range of command sequences and reprogramming options. Conversely, a "Patient" programmer is limited to "Status Check", "Return to Low" (equivalent to "Start Low") and "Program Meal (high) Dose".

Each programmer command sequence is structured to simplify the programmer operation and to minimize the probability of error by the operator. The longest command sequence in the "Patient" programmer ("Program Meal Dose") is given here for illustrative purposes. The patient is not given the option to reprogram the low rate. Thus, after entering the desired high dose into the programmer via the keyboard, the patient presses the "Transmit" button. This begins transmission of the command sequence for "Program Meal Dose", which consists of a "Status Check" to determine the implant's current low rate, a "Reprogram" to re-enter the current low rate and enter the new high dose, a "Start Low" to preset the High Dose Counter, a "Start High" to begin the high dose, and a "Status Check" for verification. The entire sequence of five commands and two replies takes three seconds to complete, and is followed by an audible beep. All command sequences but "Beeper On" end with a "Status Check" and an audible beep, indicating a successful and complete transmission sequence.

Operation of the implant electronic control is as follows: Rate or dose information is retrieved from the Program Register (refer to Figure 6) by the Program Select buffer, according to the setting of the High/Low latch. The rate (Low state) or dose (High state) information is then presented the Program Counter which controls the rate of output pulses to the pump. The system operates at low rate unless a Start High programmer command set the High latch. This command also enables the High Dose Counter. When the programmed dose has been delivered, the low state is set, reinitiating low rate delivery. The system operates in either the low or high mode at all times, unless a Reset/Stop command or a parity error inhibits pump output by stopping the Program Counter.

The Dose Counter counts pump pulses and delivers this information to the Status Register. During a Status Check, this pulse count information is translated to units of insulin by the programmer.

The implant also gathers battery and flow diagnostic data. A low battery detector makes a threshold voltage measurement at the maximum load time for the battery (coincident with the trailing edge of the pump output pulse). If the voltage is below a predetermined level, a latch is set and this information is presented to the Status Register. The voltage status is updated with each pump output pulse. A rudimentary Flow Detect circuit monitors a set of switch contacts in the pump and compares the number of electrical pulses delivered with the actual pump rotation. This circuit can detect a 10° error in pump rotation, which may result from mechanical failure or from a battery voltage that is too low to consistently operate the pump. Once an error is detected, it is presented to the Status Register and can only be cleared by a Stop/Reset command.

The implanted systems have 15 low rates and 15 high doses which are programmable. With U100 insulin, the present implants have low rates ranging from 5.9 units/hour to 0.39 units/hour (15 multiples of 128 seconds/pulse, with 0.21 units of U100 insulin delivered per pulse), and high doses ranging from 0.84 U to 12.5 U (15 multiples of 64 seconds of high dose delivery, at 16 seconds/pulse, U100 insulin). The range of rates and doses can be varied up or down by multiples of two, by jumper wire changes in the implant control.

Power Supplies. The implant module and the external programmer are each powered by two hermetically-sealed 3.66 V lithium-thionyl chloride AA-size cells in a series connection. Both Tadiran and GTE cells have been used (Tadiran, Plainview Electronics, Plainview, New York; GTE Sylvania, Communications Systems Division, Waltham, Massachusetts). These cells are rated at 1.8 amp-hours capacity at 10 to 20 mA current. In later implant

modules, a capacitor discharge unit consisting of two 850 μF, 8 V tantalum-cased tantalum capacitors (Type 135D, Sprague Electric Co., North Adams, MA) trickle-charged by the lithium cells, is used to power the implant electronics and pump.

Enclosure. The implant module components are housed within a two-compartment sealed titanium enclosure. The two enclosure halves are drawn from 0.5 mm thick sheet stock and the centrally-located transverse header plate from 0.75 mm thick stock. The electronics, communication coil, and batteries are housed in one half of the enclosure, which is laser-welded to the header plate to provide a hermetically-sealed compartment. Electrical connections to the pump are made via hermetic single electrode feedthroughs in the header plate (Hittman Materials and Medical Components, Columbia, MD). The pump is attached to the opposite side of the header plate from the electronics with mounting brackets. The pump tubing connects to the reservoir and to the delivery catheter through titanium tubing feedthroughs brazed to the wall of the pump enclosure. The pump enclosure is sealed to the header plate with epoxy, and the implant module covered with Silastic. A porous Dacron mesh flap attached to the enclosure is provided for suturing and to permit tissue ingrowth.

Reservoir, Tubing and Catheter. The insulin reservoir, pump tubing, and delivery catheter are all fabricated from medical-grade silicone rubber. The reservoir is a 5 ml capacity, discoid-shaped pouch which has an integral hard plastic (polystyrene) needle stop and septum holder. A silicone rubber septum is used for percutaneous filling of the reservoir using a 25 gauge hypodermic syringe. Figure 7 shows the insulin reservoir diagrammatically, including the refill septum and septum holder. The refill septum is 3 mm thick silicone rubber sheet material used for gas-chromatograph septa (HGC-140, Analabs, Inc., North Haven, CT). It is cut 5% oversize to provide a compression fit in the septum holder. The top and bottom walls of the reservoir are fabricated from 0.25 mm thick Silastic

sheet sealed together and to the other components with Silastic Medical Adhesive Silicone Type A (Dow-Corning, Midland, MI). Connecting tubing from the reservoir into the implant module is 0.7 mm ID x 2.4 mm OD silicone rubber (Sil-Med Corp., Taunton, MA). The tubing used in the peristaltic pump is 1.5 mm ID x 3.0 mm OD silicone rubber (Sil-Med). The insulin delivery catheter is a modified Silastic cerebrospinal fluid peritoneal catheter (Dow-Corning), with a low-pressure slit valve at the delivery end.

III. Methods

The quasi-static torque output of the rotary solenoid was measured with an Instron Tensile Tester Model 1122, as the solenoid was allowed to move incrementally while being energized from a constant current source at 300 to 500 milliamps. Torque requirements of the return spring and the pump head were also measured quasi-statically with the Instron tester, using various tubing sizes and materials.

Pump flow measurements were made using two techniques. For pulse-to-pulse delivery-volume comparison, the displacement of water pumped into a vertical precision-bore capillary tube (1.07 mm ID) was measured following each pulse using a cathetometer. This test arrangement was also used with air pressure applied to the capillary tube exit to test for flow characteristics at applied pressures to 300 kPa (45 psig).

To characterize more accurately the average delivery volume per pulse, water was pumped at various delivery rates into a weighed collection bottle. The collection opening was made small to minimize evaporation losses. After a measured number of pulses (typically greater than 5,000), the bottle was reweighed and the mass of water converted to volume using standard density tables.

Reliability of the electronic controls was established at the leadless hermetic package level (LHP), according to Mil Standard 883, including internal visual inspection, baseline electrical inspection, temperature cycling (10 cycles from -55° to +125°C), acceleration, fine and gross leaks, and burn-in to zero failures (160 hours at +125°C) with bias. The LHP's were then assembled on a previously tested ceramic substrate (Figure 5) in a vapor phase reflow soldering operation which resulted in a high-yield assembly. This process was developed by and performed by RCA at Moorestown, NJ.

A Rockwell AIM 65 microcomputer with an interface adapter was used to test the programmers for proper operation. Most of the testing was fully automatic. This phase of testing verified correct parity, reprogramming, and proper operation of the cumulative dose count. The second phase of testing was operator-interactive and used the communication coil for all tests. Proper operation of the transmitter/receiver, error codes, display, and program rates was verified.

Lithium-thionyl chloride cells were evaluated in the laboratory for both the implant module and the external programmer applications. For the implant application, cells with and without the capacitor discharge unit were evaluated at 39°C either open circuit or using a tester which provided a constant 50 μA load current to simulate the electronic control current requirement, and a pulsed inductive load at 4.25 minute intervals to simulate the pump requirement. Accelerated cell lifetime testing was performed using a similar tester which provided a higher constant load current (1.2 mA) and a simulated pump load at 16 second intervals. Other cells were maintained at room temperature either open circuit or with a 50 μA steady current to test their suitability for use in the remote programmer. At several day intervals, the voltage and current profiles were monitored on an oscilloscope during a pulsed load condition. Some cells were

preconditioned prior to testing by discharging through a 15 ohm load for several minutes, until a constant load voltage was attained. The preconditioning, which reduces the cell capacity by 1-3%, removes from the anode a passivation barrier which forms during storage, and which otherwise may limit the maximum discharge current. Cells were not preconditioned for the capacitor discharge unit tests, in which lower currents were acceptable.

The mechanical integrity of reservoirs to be implanted was determined by visual inspection and by leak testing at modest pressure. Leak-tightness was tested by overinflating the reservoirs with air (200% of normal capacity), submerging in water, and looking for the formation of air bubbles. Other reservoirs were subjected to more severe static pressure tests using a Tinius/Olson Lo-cap testing machine to provide pressure on the water-filled reservoir via two flat plates. Pressure was applied in a linear ramp for 50 seconds to a maximum of 400 kPa (60 psig) and held at or near maximum pressure for an additional 120 seconds. The applied pressure was measured using a Kulite 100 psi semiconductor strain gauge attached to the exit tubing of the reservoir.

In-vitro environmental testing of the implant components was accomplished in a 100 percent relative humidity, CO_2-enriched (6%), 39°C environmental test chamber. Both pump and electronic control response to the environment were measured weekly under normal operating conditions. Dynamic test parameters measured included electronic control current at a variety of operating voltages and accuracy of delivery rate timing. Pumps were examined periodically for wear and corrosion.

In vivo testing of the implant modules was accomplished at the Animal Resource Facility of the University of New Mexico using alloxan-induced diabetic mongrel dogs.[10] System data gathered included battery lifetime under implant conditions, electronic control functioning, and accuracy of

delivered fluid volume. The apparent fluid volume delivered between refills was determined from the implant electronics Dose Counter, which is interrogated at each refill. The apparent volume was compared with the actual delivered value, which was determined by withdrawing the reservoir contents prior to refill and comparing with the fluid volume originally added.

IV. Results

Torque Measurements. Figure 8 shows the quasi-static torque output of the rotary solenoid at several current levels. The torque curves are typical for the type of solenoid poles employed and the limited angular motion of the rotor between mechanical stops. The lower curve shows the torque required to drive the pump head when loaded with silicone elastomer tubing. (This includes also the solenoid return spring requirement.) The adequacy of torque output indicated by the quasi-static measurements was confirmed in dynamic tests in which normal pump operation was observed at all current levels exceeding 230 milliamps. In the implant, current levels typically are 300 - 400 mA (see Figure 11).

Studies of the effect on torque requirement of tubing material, tubing-wall thickness, and tubing compression beyond the pinch-off height were performed using latex and silicone tubing. Pinch-off height is defined here as the maximum distance from roller to outer pump head surface at which no back flow occurs through the pump tubing at any roller rotational position at 50 kPa (7 psig) exit pressure. Table I lists the physical characteristics of three tubing sizes and the resulting peak torque requirement with a roller-to-head spacing 0.061 mm less than pinch-off height in each case. Also shown for one tubing size is the effect of tubing compression (the roller-to-head spacing was decreased from 0.61 mm to 0.163 mm less than pinch-off height). Changes in tubing-wall thickness or in compression beyond pinch-off change the torque requirements of the

pump head. These changes are small in relation to the torque output of the rotary solenoid, however, and do not affect pump performance nor power requirements noticeably. The silicone rubber tubing required slightly higher torque than the latex tubing. For the implants, only silicone rubber tubing has been used.

Flow Measurements. Figure 9a shows the delivery volume for each 10-degree increment of rotation for a commercially-available, single roller peristaltic pump. This pump uses 1.5 mm ID x 3.0 mm OD Tygon tubing. Figure 9b shows comparable data for the three-roller pump head developed for the present insulin delivery system using the silicone tubing. Data from more than one revolution is shown, demonstrating the degree of reproducibility of delivery volume as well as the uniformity from pulse to pulse. Pressurizing the fluid at the outlet was found to have little effect on the delivery volume for the three-roller pump until pressures greater than 200 kPa were applied. At these pressures, the tubing distortion was sufficient that fluid would flow back past the rollers on some pulses.

Studies of the delivery volume averaged over several thousand pulses showed a variation of less than 3 percent for the heavier wall latex tubing in five trials (1.44-1.48 microliters per pulse average). The tubing was reloaded in the pump head before each trial. The variation in average delivery volume for different tubing sizes was from 1.44 microliters per pulse for the heavier wall latex to 2.15 microliters per pulse for the silicone tubing. No variation in average delivery volume was noted with pulse repetition rates from 1/min. to 120/min.

Two-Way Communication. Coupling between the remote programmer and the implant communication coils provided a maximum communication range of about 150 mm (6 inches). A minimum induced signal amplitude of 25 mV was

required for communication. The signal amplitude requirement and 8-bit ID code are advantageous in avoiding interference from electromagnetic sources. In the current version of the implant control, it has not been possible to upset the internal program or the implant operation by electromagnetic noise signals from electric drills, hair dryers, televisions and other appliances operated more than 2 cm (about 1 inch) from the implant module.

Power Supply Measurements. Operating current for the implant electronic control as a function of applied voltage is shown in Figure 10. In the implant, two lithium-thionyl chloride cells in series provide approximately 7.3 V which results in a current drawn by the control of 50 to 55 microamps. This results in a consumption of approximately 1.3 mA·hr/day from each cell.

Figure 11 shows current and voltage waveforms during the pump pulse for direct discharge from the cells (11a) and for discharge from capacitors (11b). Energy usage in each case is approximately 65 mJ/pulse, including cell internal losses or losses in the capacitor charging resistor. With 250 pulses per day (equivalent to 50 units of U100 insulin), the pump pulses represent an additional 0.6 mA·hour/day consumption.

Adding the electronic control and pump pulse requirements, a cell lifetime of 31 months is calculated if the theoretical cell capacity of 1.8 amp·hour is assumed. However, due to the formation with time of a passivation layer of LiCl on the lithium electrode of the cells, their high pulse current capability may be impaired. Figure 12 demonstrates the performance during a pulsed load of Tadiran and GTE lithium-thionyl chloride cells as a function of time at 39°C. Half of these cells were maintained open circuit between test pulses and maintained with dc loads. As shown, the ability of the cells to provide a high-current pulsed discharge

without excessive voltage drop degrades with time, though it is clearly enhanced for cells with a dc load which reduces the rate of formation of the passivation layer.[11]

The implant application requires that two cells in series be capable of sustaining a voltage greater than 3.5 V during a pulse in order to provide sufficient current for pump operation. The data indicate that because of passivation, the cells may allow satisfactory pump operation in the implant environment for only a few months, which represents a small fraction of the battery capacity (10-20%). Alternatively, use of a trickle-charged Capacitor Discharge Unit (CDU) to provide the pump pulse substantially reduces the maximum current requirement from the cells, and thus makes the presence of a passivation layer less important. Using a 300-ohm series charging resistor, the maximum current from the cells following a pump pulse is 16 mA, easily supplied even with substantial passivation buildup. Figure 13 shows results from accelerated life tests of Tadiran and GTE cells with a 1700 μF CDU. In each test, the pulse rate and the steady current were increased 22 times from normal values (to 5000 pulses/day, 1.2 mA steady current). Equivalent cell lifetimes from 28 to 43 months were attained. Real-time capacitor discharge studies in progress have shown no degradation of pulse current levels after 120 days.

For the external programmer, battery requirements are less severe. The programmer electronics requires 7 mA. Transmission pulses are 2 or 8 ms at 100 mA. A major difference in the programmer and the implant applications is the use temperature, approximately 20-25°C and 37°C, respectively. Figure 14 shows performance data under pulsed load for Tadiran and GTE cells at 23°C. A comparison of Figures 12 and 14 shows that passivation is a much less severe problem at room temperature than at implant temperature. With a high-resistance shunt, these cells are totally satisfactory for use in the remote programmer.

Reservoir. In static pressure tests, the silicone rubber reservoirs did not fail, leak, or show any damage at applied pressures of 400 kPa (60 psig). In a separate experiment, 50 punctures of the silicone rubber septum in a reservoir were made using a standard point 22 gauge needle. In a subsequent pressurization underwater, no leaks were detected.

In Vitro Environmental Testing. Pump components, both plated and unplated, were exposed to 100 percent relative humidity and 39°C in a CO_2-enriched atmosphere. After five months, visual microscopic examination of the components at 40X showed considerable pitting and corrosion of unplated Hyperco-50 rotor and stator parts. Electroless-nickel plated parts showed almost no corrosion. Based on these results, the electromagnetic components of all implanted pumps are now electroless-nickel plated for corrosion resistance.

In twelve months of similar environmental testing of three electronic controls and one pump, no changes in control current usage, control function or pump operation were noted. When removed from the environmental test, the electronics still functioned normally and the pump showed no noticeable wear of any components. A total of 20,000 pump pulses occurred during this test.

In separate accelerated life tests of the pump in the laboratory (25°C), 4.5 million pump cycles were recorded. A slight galling of the brass ratchet wheel was noted between one and two million cycles, the equivalent of 11 to 22 years normal use. The silicone rubber tubing was slightly distorted in cross-section following the test, and some microscopic cracking of the tubing inside surface was noted.

In Vivo Tests. The systems described have been implanted in six diabetic dogs and used to maintain blood glucose control in the animals for

periods ranging from one to three months. In all cases, blood glucose control was improved, although no attempt was made in these experiments to optimize control.[10] The system has recently been implanted in one diabetic human.[12]

Although insulin precipitation in the reservoir or catheter has been reported by others[13,14] and experienced by us in preliminary studies, no problems with insulin precipitation have been experienced during the present implant studies using buffered Lilly neutral regular insulin. Our insulin precipitation studies are described in more detail elsewhere.[15]

The implanted systems functioned appropriately and accurately except for one instance of moisture-induced electronics failure in an epoxy-sealed unit. Subsequent units with hermetically-sealed (laser-welded) electronics enclosures have functioned without problem. Delivered insulin volume, measured at regular refill intervals of one week, was within measurement accuracy (plus or minus 0.1 ml) except for one dog study in which leakage through the pump was detected. This problem was solved by providing a tighter occlusive seal of the tubing within the pump head in subsequent units.

Additional study of the unit which leaked showed the leak rate to be proportional to the pressure within the insulin reservoir. To minimize this driving force, the reservoir design was modified from a flat pouch to the shallow conical shape shown in Figure 7. This change reduced the maximum pressure in the reservoir from 27 Torr (flat pouch) to less than 1 Torr (conical shape).

In the first five dog implants, the pumps were driven directly from the lithium batteries. In each implant, a steady degradation of battery performance with implant time was noted, due to a passivation layer buildup. In three of the five implants, battery voltage under pulsed load

had dropped from an initial 5.0 V to 3.7 V (an internal voltage check point) within two months. In the latest two implants (one dog, one human) a capacitor discharge system is used to drive the pump. The systems employing a capacitor discharge unit have not been implanted sufficiently long to determine an actual lifetime in vivo.

V. Discussion

Although external insulin delivery systems offer advantages of simplicity and ease of maintenance, they do pose certain biological safety issues related to the necessity of percutaneous insulin delivery. For long-term studies, especially those related to intravenous or intraperitoneal insulin infusion, an implantable insulin delivery system has safety advantages. The development of an implantable insulin delivery system is a logical extension of our earlier development activities in the external insulin delivery system.[16]

Earlier studies of a prototype implantable system[7] revealed several limitations which have been addressed in the present system. First, the cells used in the prototype ($Li-SO_2$) were pressurized and not safe for an eventual human implant application. These have been replaced in the present system by unpressurized $Li-SOCl_2$ cells, with extensive implant applications in early cardiac pacemakers. The prototype system was much heavier than the present system (450 g vs 280 g). The range of delivery rates was very limited previously (one high and three low rates), and is now much broader (15 high doses, 15 low rates). Two-way communication has been developed in the present system, providing a range of previously unavailable diagnostic data from the implant module (battery status, delivery rate, cumulative dose, flow error). Potential battery lifetime has increased from 6 to 30-40 months. Identification coding of transmitted data has been added, providing additional safeguards against reprogramming by spurious electromagnetic signals.

Initial observations with the present implantable insulin delivery systems have been encouraging. Remote programming of delivery rates and interrogation of delivery status have proven to be relatively straightforward and highly successful. The implantable electronic controls function very satisfactorily as long as they are maintained in a dry environment, and battery performance has been satisfactory over a period of several months. Overall system performance has been good and it has been possible to maintain relatively normal blood glucose in the test animals over extended periods of time. However, there are still several problem areas. Corrosion of magnetic rotary solenoid parts, while minimized by plating, has not been totally eliminated. To provide an extended lifetime pump, more study in this area will be required. Due to the passivation behavior of present lithium-thionyl chloride cells, long-term performance has been poor. Use of a capacitor-discharge system should eliminate the high-current requirement for cells. Alternatively, it appears likely that in the near future, superior cells based on passivation-resistant lithium cell chemistries will be available. Implant lifetimes of several years appear probable. The implantable insulin reservoir is one of the most vulnerable aspects of the present system, and alternative reservoir designs need to be considered. A reservoir located within the implant module appears to offer maximum safety and simplicity, although control of reservoir pressure inside the sealed module may be difficult. In the future, it will be desirable to fabricate electronics with data store redundancy and with improved monitoring capabilities. This will require large-scale-integrated circuit or microprocessor technology in order to maintain small size and high reliability. Leakage problems in the pump represent a safety concern in the present implant system, and are being studied. Finally, miniaturization of the pump will be an important part of further advances in implant technology. Smaller systems are especially needed for females and youth recipients.

References

1. A. M. Albisser, "Devices for the Control of Diabetes Mellitus," Proc. IEEE 67, pp. 1308-1320, 1979.

2. W. J. Spencer, "A Review of Programmed Insulin Delivery Systems," IEEE Trans. Biomed. Engr. BME-28, pp. 237-251 (1981).

3. V. I. Shumakov, "Comments," Trans. Amer. Soc. Artif. Intern. Organs 21, pp. 521-522, 1975.

4. L. J. Thomas and S. P. Bessman, "Prototype for an Implantable Micropump Powered by Piezoelectric Disk Benders," Trans. Amer. Soc. Artif. Intern. Organs 21, pp. 516-520, 1975.

5. P. R. Perkins, F. D. Dorman, T. D. Rohde, P. J. Blackshear, P. L. Blackshear, Jr., R. L. Varco, and H. Buchwald, "Design and Initial Testing of a Totally Implantable Transcutaneously Controllable Insulin Delivery Device," Trans. Amer. Soc. Artif. Intern. Organs 24, pp. 229-231 (1978).

6. K. Prestele, K. Geisen, M. Franetzki, S. Jung, and E. Reif, "A Remote-Programmable, Implantable Insulin Delivery Device: Technique and Results of Animal Experiments," presented at the Islet-Pancreas Transplantation and Artificial Pancreas Satellite Symposium, Vouliagmeni Beach, Greece (Sept. 22-23, 1980).

7. G. A. Carlson, J. T. Love, R. S. Urenda, R. E. Bair, W. J. Spencer, J. M. Shuck, R. D. Eaton, D. S. Schade, and P. W. Day, "Development of an Artificial Beta Cell Suitable for Animal Implantation," Trans. Am. Soc. Artif. Intern. Organs 26, pp 523-526 (1980).

8. G. A. Carlson, B. D. Shafer, R. S. Urenda, W. J. Spencer, R. C. Sadler, and R. P. Eaton, "A New Low-Power, High-Reliability Infusion Pump," Proc. 7th Annu. New England (Northeast) Bioengineering Conf., Troy, NY, pp. 193-196, 1979.

9. Albisser, A. M., Jackman, W. S., Ferguson, R., Bahoric, A., Goriya, Y., "A Portable Precision Pumping System for Chronic, Programmed Insulin Infusion," Med. Progr. Technol. 5, pp 187-193, 1978.

10. D. S. Schade, R. P. Eaton, B. McDowell, R. Kubica, E. Vaughn, G. A. Carlson, and W. J. Spencer, "Total Implantation of an Insulin Delivery Device,"Hormone and Metabolic Research, in press, 1981.

11. M. L. Kronenberg, "Experimental Methods Used to Compare Cathode Formulations and to Monitor Passivation Build-up in Lithium Cells", Symposium Proceedings, Power Sources for Biomedical Implantable Applications, Ed. by B. B. Owens and N. Margalit, 1980.

12. D. S. Schade, R. P. Eaton, W. S. Edwards, R. C. Doberneck, W. J. Spencer, G. A. Carlson, R. E. Bair, J. T. Love, R. S. Urenda, and J. I. Gaona, Jr., "Successful Short-Term Implantation of a Remotely-Programmable Insulin Delivery System in Man", J. Amer. Med. Assoc., In Press 1981.

13. K. Irsigler and H. Kritz, "Long-Term Continuous Intravenous Insulin Therapy with a Portable Insulin Dosage-Regulating Apparatus", Diabetes 28, pp. 196-203, 1979.

14. A. M. Albisser, W. Longheed, K. Perlman and A. Bahoric, "Nonaggregating Insulin Solutions for Long-Term Glucose Control in Experimental and Human Diabetes", Diabetes 29, pp. 241-243, 1980.

15. D. S. Schade, R. Philip Eaton, J. DeLongo, L. C. Saland, A. J. Ladman and G. A. Carlson, "Electron Microscopy of Insulin Precipitates", to be published in Diabetes Care.

16. G. A. Carlson, J. T. Love, R. S. Urenda, W. J. Spencer, and R. P. Eaton, "A Portable Insulin Infusion System with a Rotary Solenoid Driven Peristaltic Pump," Med. Prog. Technol. 8, pp. 49-56, 1980.

TABLE 1

Torque comparisons for latex and silicone elastomer tubing in the rotary solenoid pump head

Material	Latex	Latex	Silicone
Outside diameter (mm)	3.28	3.02	3.25
Inside diameter (mm)	1.40	1.58	1.63
Wall thickness (mm)	0.94	0.72	0.81
Pinch-off height (mm)	1.42	1.22	1.45
Peak torque at 0.061 mm less than pinch-off height (N·m)	0.0034	0.0022	0.0044
Peak torque at 0.163 mm less than pinch-off height (N·m)	0.0058		

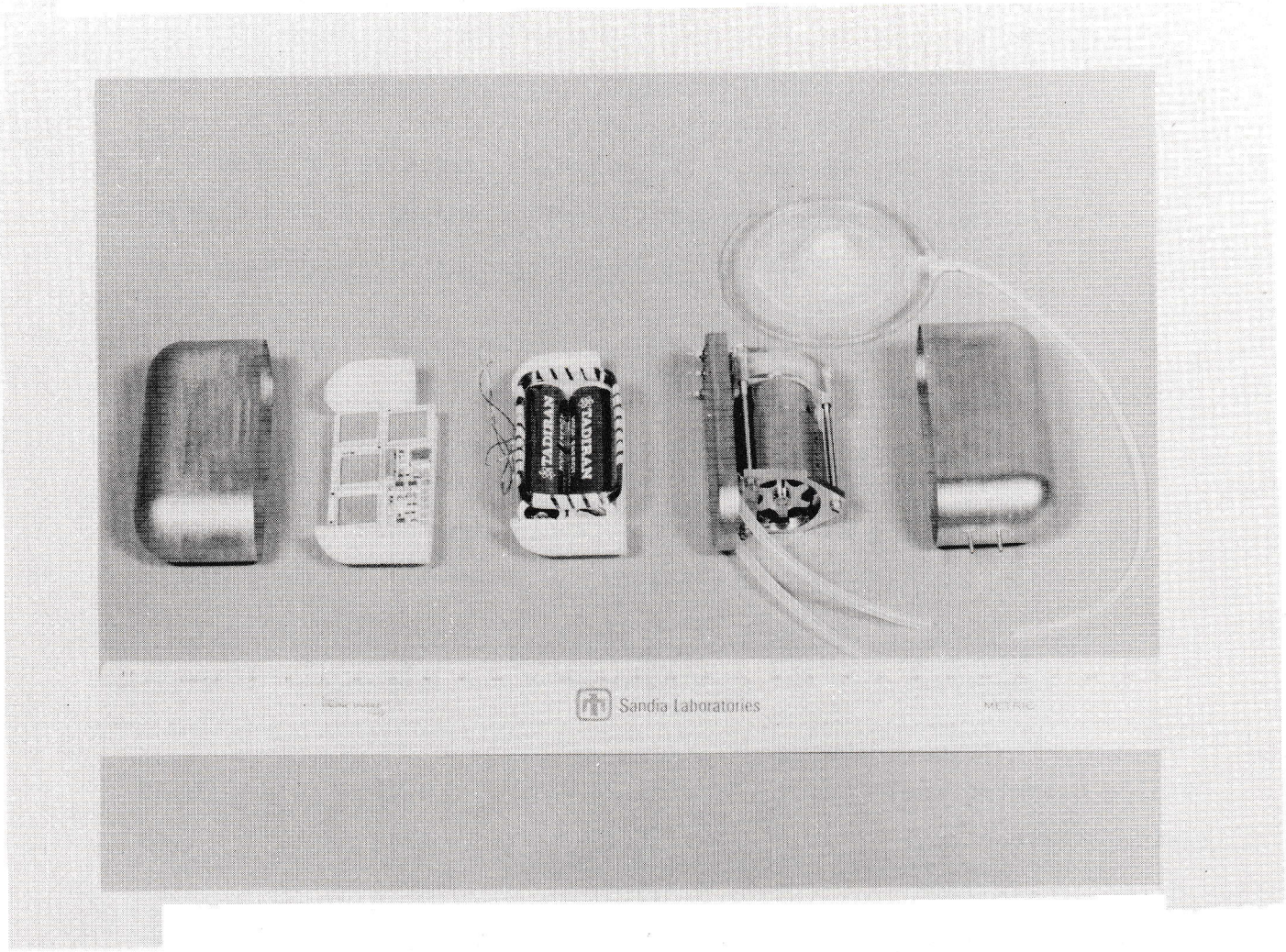

Figure 1. Exploded view of implantable insulin delivery system showing, from left, titanium enclosure (left half); electronic control; cells and energy storage capacitors nested in communication coil; peristaltic pump mounted on a titanium header plate; and titanium enclosure (right half) with tubing feed throughs. In front are the insulin reservoir and a simulation of the delivery catheter.

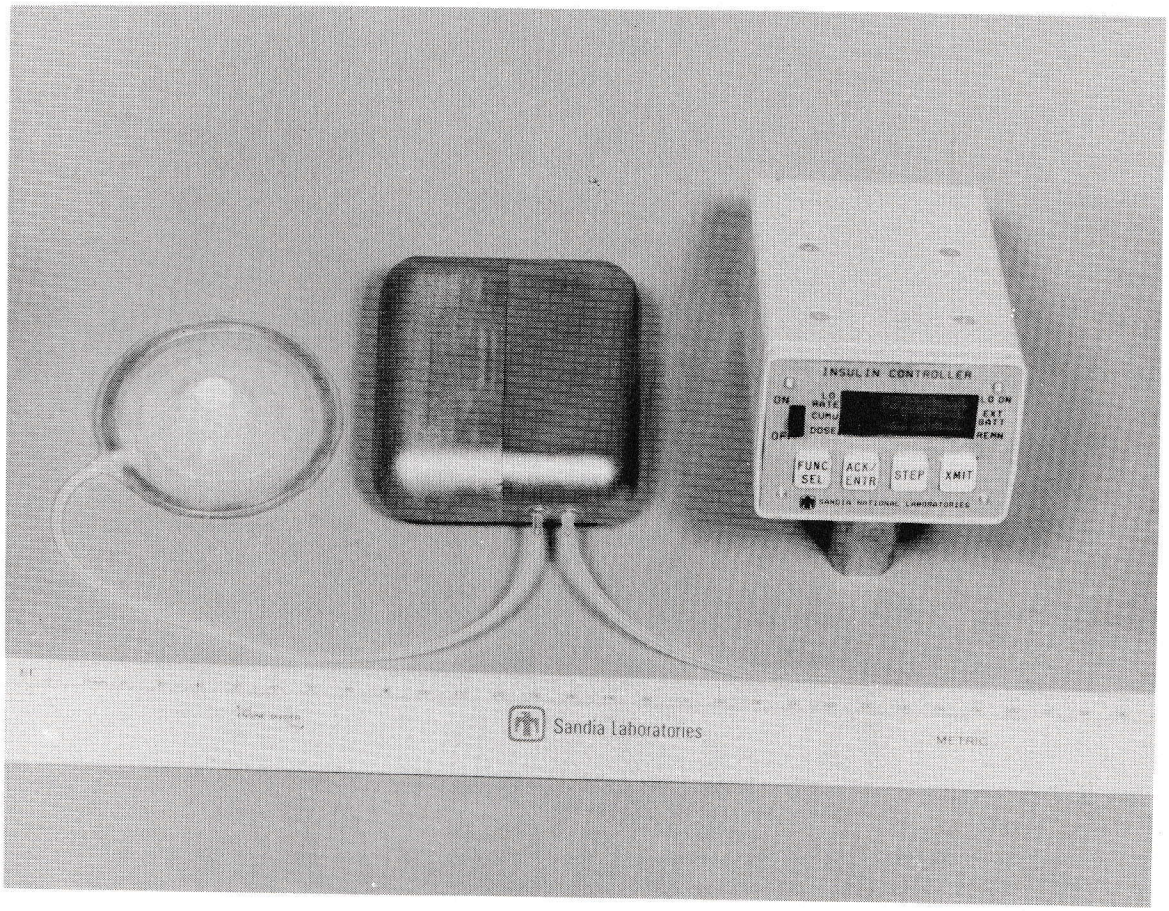

Figure 2. Implantable system and external controller.

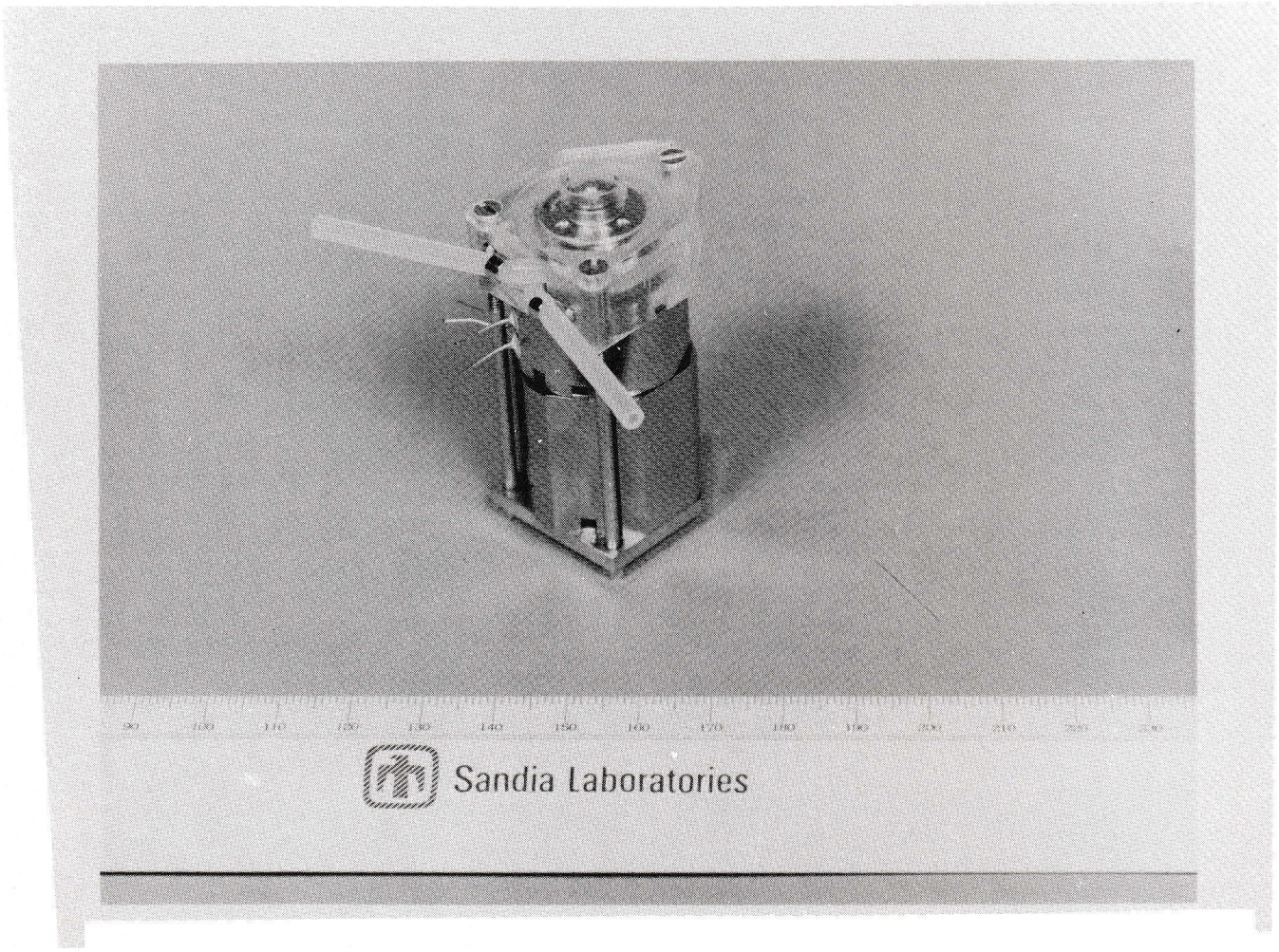

Figure 3. Rotary solenoid-driven peristaltic pump. The lucite pump head shown is replaced by stainless steel in the implant application.

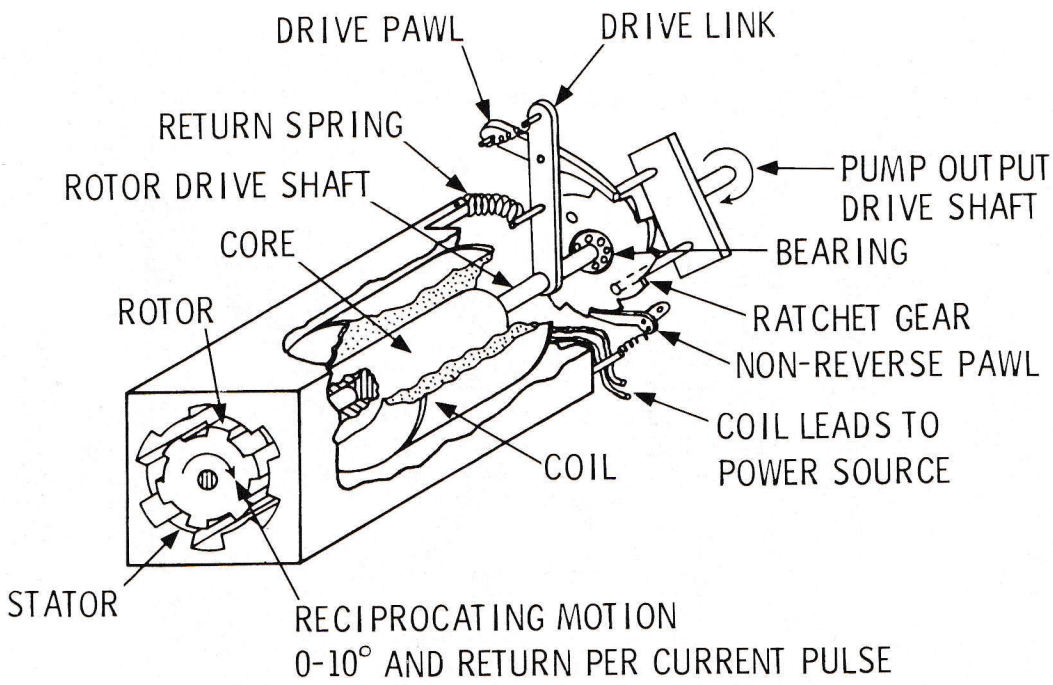

Figure 4. Schematic of rotary solenoid used to drive the peristaltic pump. An electrical impulse delivered to the coil causes the rotor to move into alignment with the stator, imparting unidirectional motion to the peristaltic pump through the drive pawl and ratchet gear.

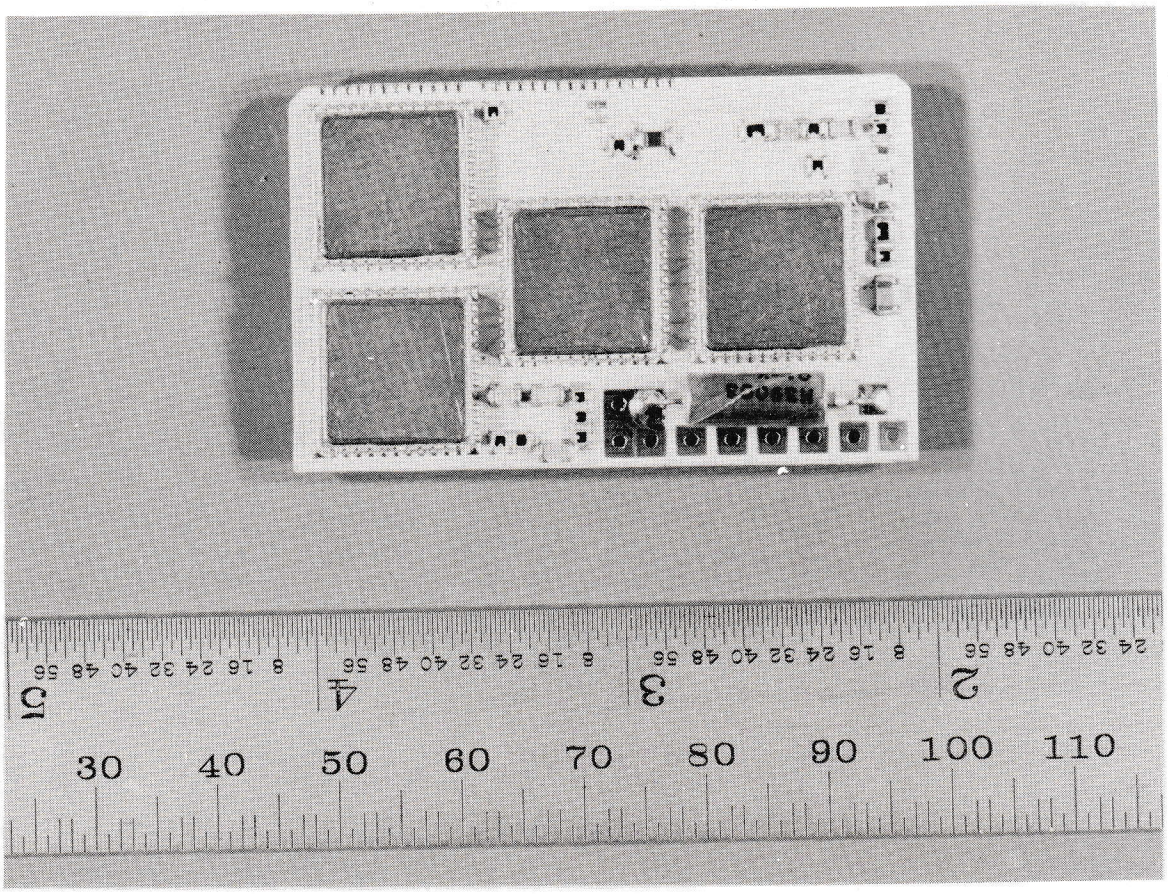

Figure 5. Detailed view of one face of an implant electronic control showing four leadless hermetic packages, numerous chip and and other components on a ceramic substrate.

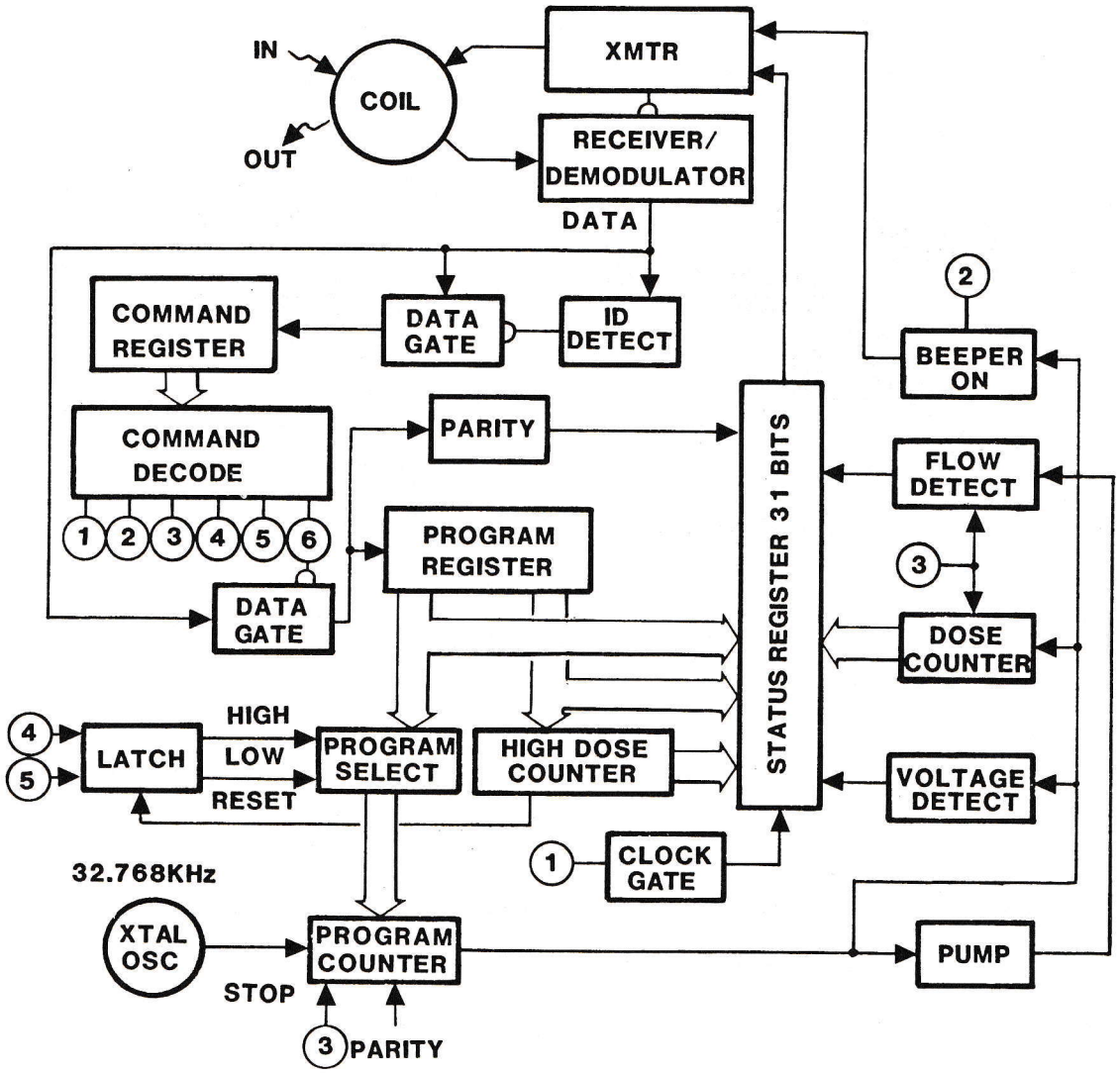

Figure 6. Block diagram of implant electronic control.

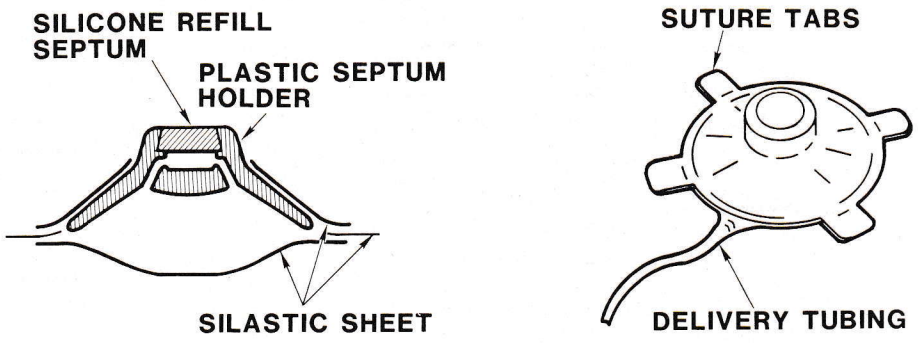

Figure 7. Insulin reservoir--schematic. At left is the reservoir in cross-section, showing the plastic septum holder with integral needle stop.

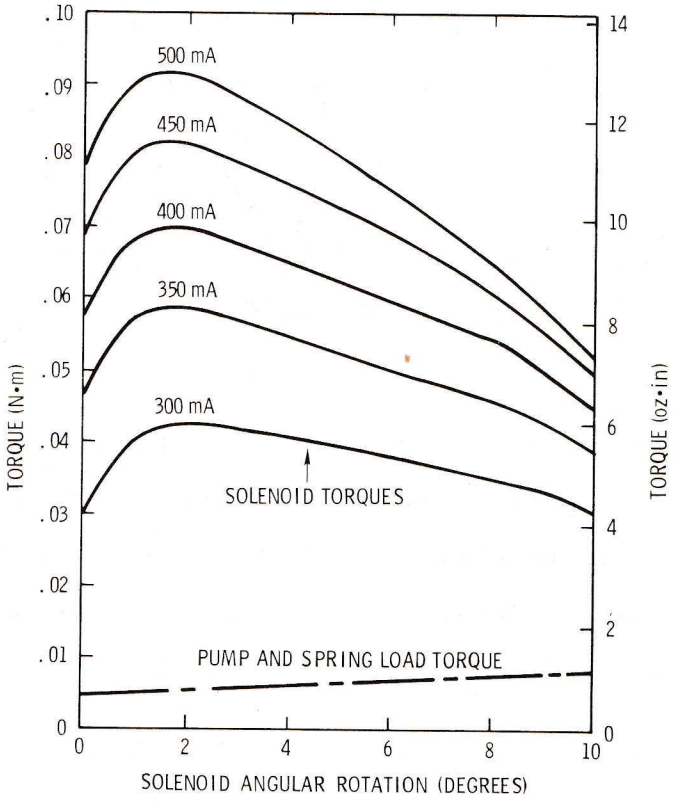

Figure 8. Torque characteristics of the rotary solenoid pump. The upper traces are the quasi-static torques produced by the rotary solenoid when driven by currents from 300 to 500 mA. The lower curve is the torque required to produce movement of the pump head and return spring. Measurements were taken over the 10 degrees rotation angle of the solenoid.

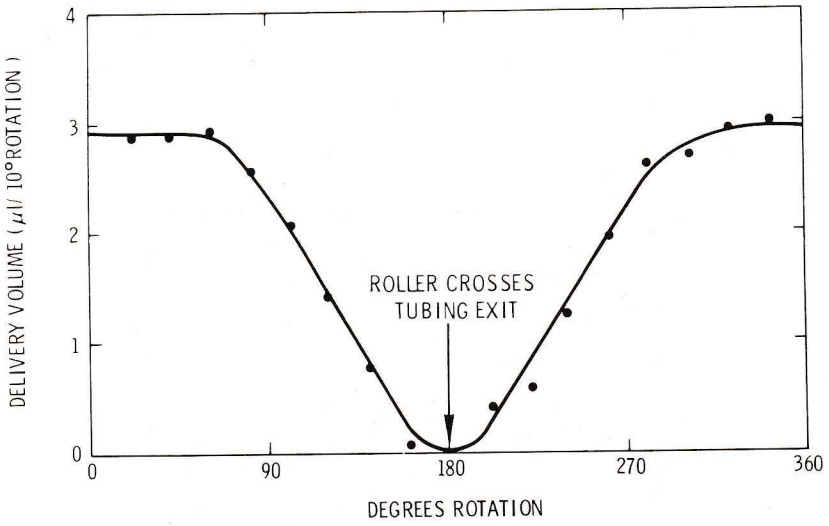

Figure 9a. Delivery volume of a single-roller peristaltic pump head over one complete rotation, showing the decline to zero as the roller crosses the tubing exit. The delivery volume has been normalized to 10-degree increments for comparison with the 10-degree pulsatile motion of the rotary solenoid pump.

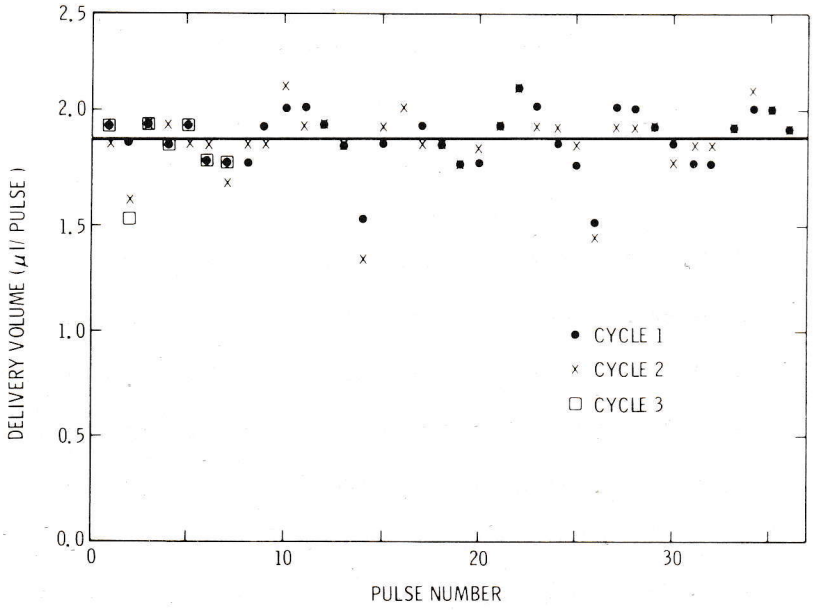

Figure 9b. Delivery volume of a three-roller peristaltic pump head over consecutive rotational cycles of the rotary solenoid pump.

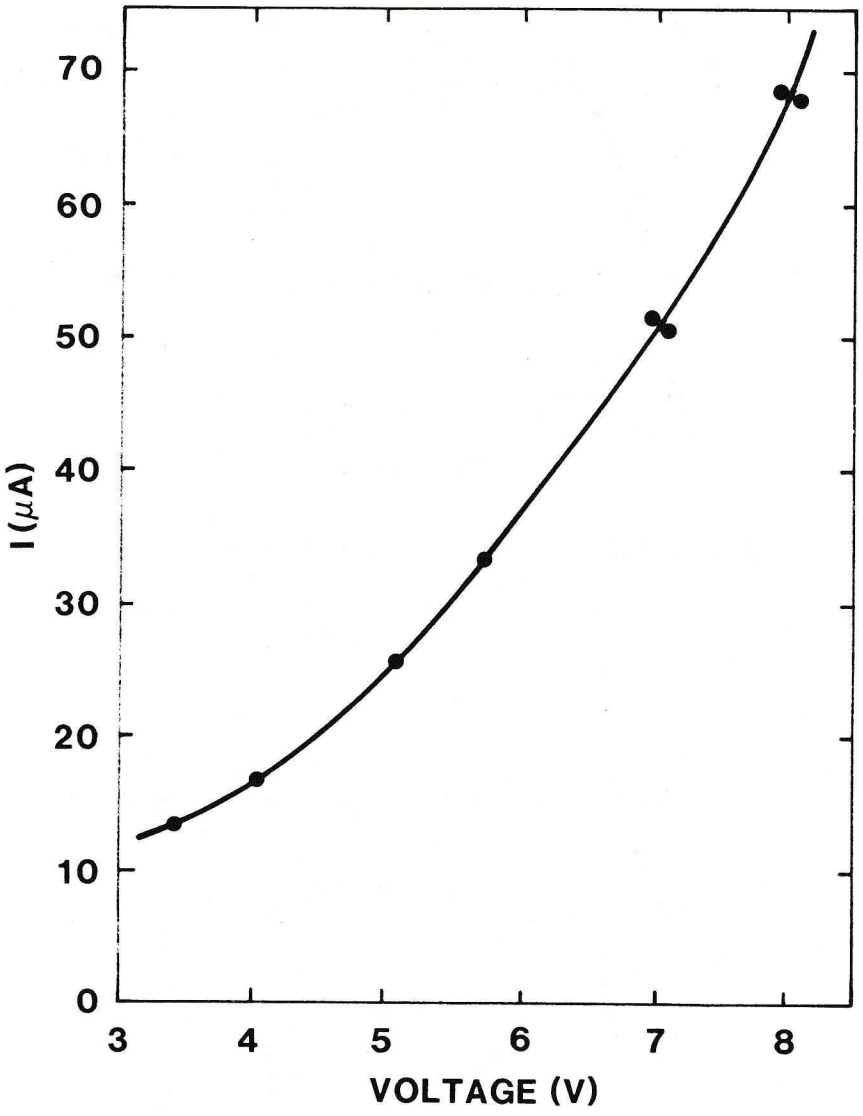

Figure 10. Implant electronic control current versus operating voltage (data from two controls).

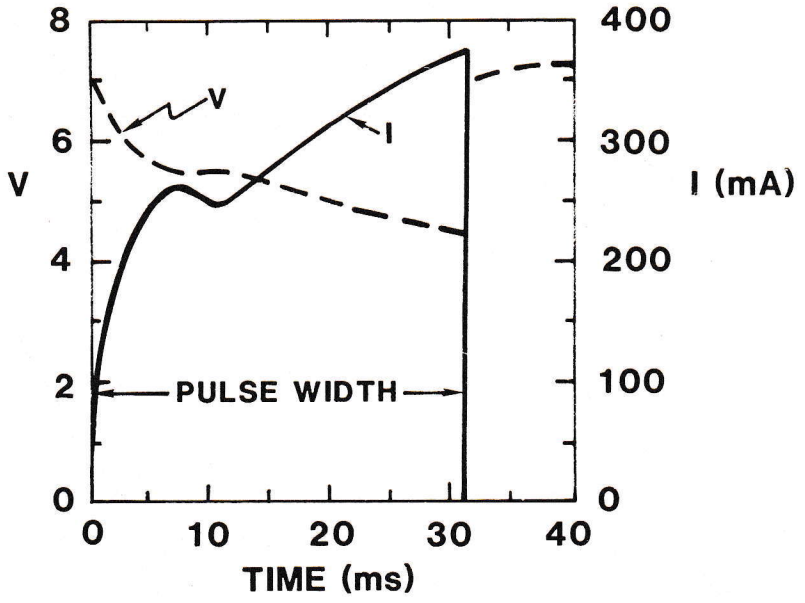

Figure 11a. Current and voltage waveforms during a pump pulse. Power supplied directly from two lithium-thionyl chloride cells in series.

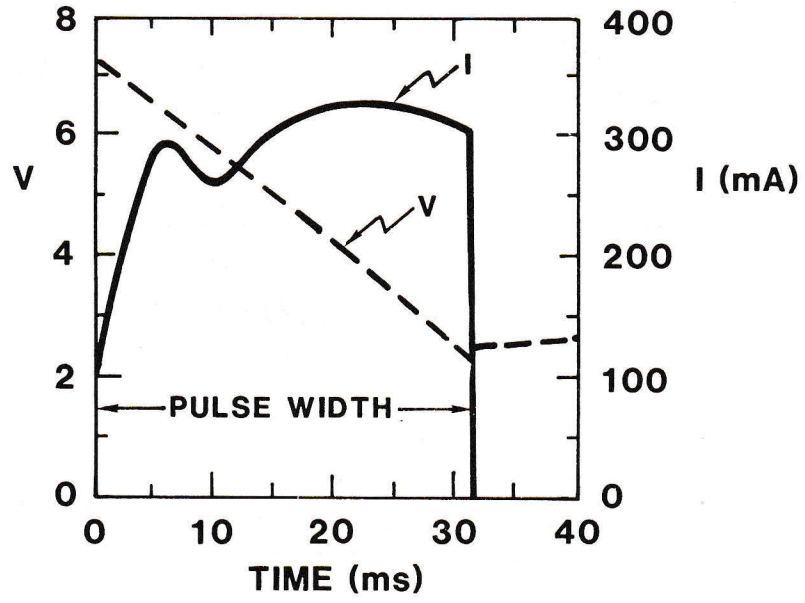

Figure 11b. Current and voltage waveforms during a pump pulse. Power supplied by a 1700 μF capacitor, trickle-charged from the same lithium-thionyl chloride cells.

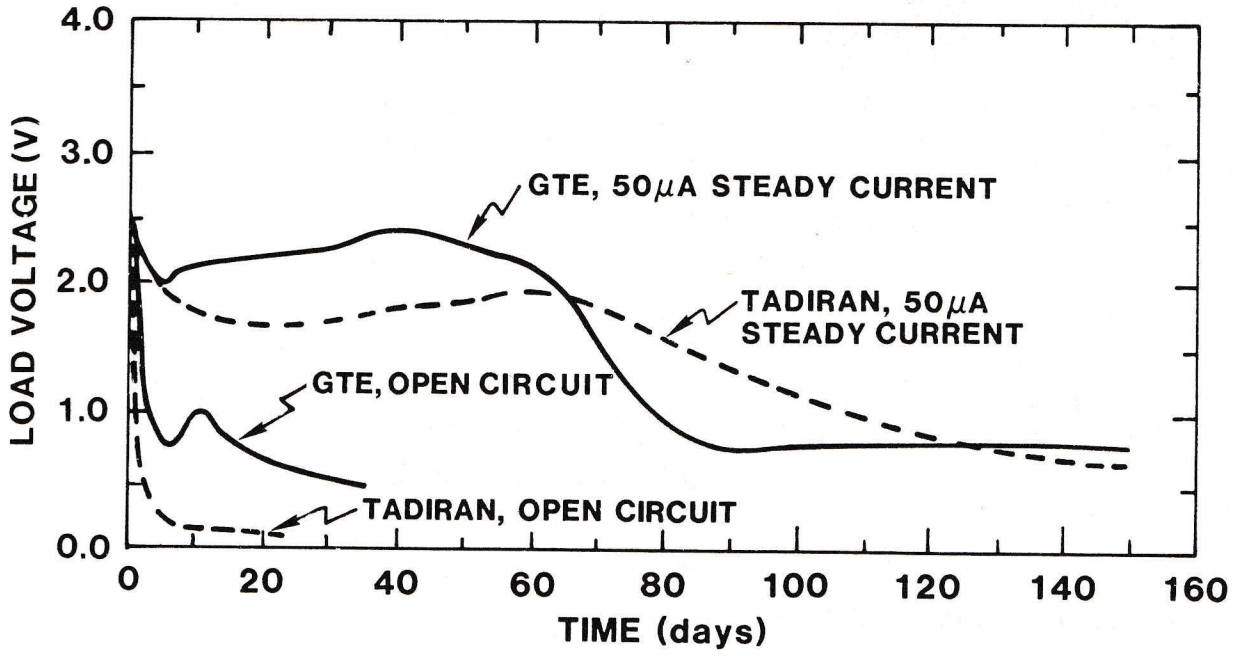

Figure 12. Minimum voltage under a simulated pump pulse load for single GTE and Tadiran lithium-thionyl chloride AA cells as a function of time at 39°C. Cells were maintained open circuit or with a resistive load throughout the study.

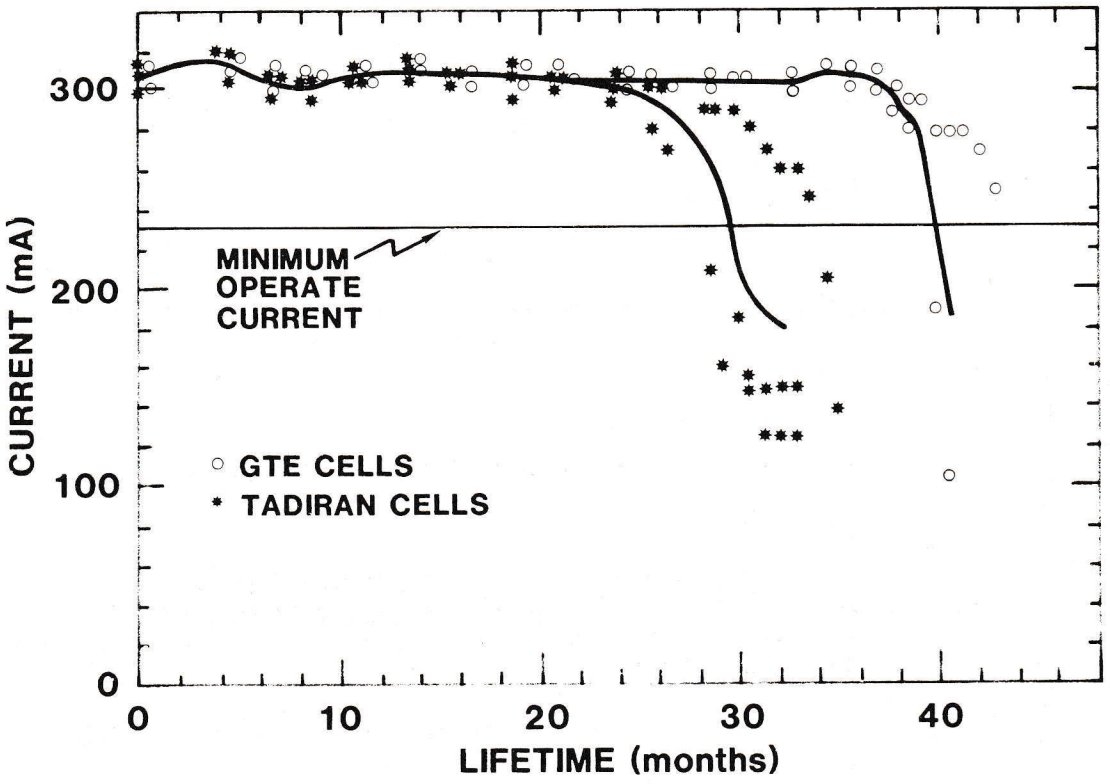

Figure 13. Apparent lifetimes of lithium-thionyl chloride AA cell pairs (series connected) at 37°C under accelerated rate conditions using trickle-charged 1700 μF energy storage capacitor discharge. Both pulsing rate and electronic control current were increased 22 times from typical implant conditions (from 250 to 5400 pulses/day; from 55 μA to 1.2 mA steady-state current). The current plotted is the final current at the end of the 31 ms simulated pump pulse. The lifetime plotted is the true test time multiplied by the accelerating factor. Solid lines are an average of three Tadiran cell pairs and of two GTE cell pairs.

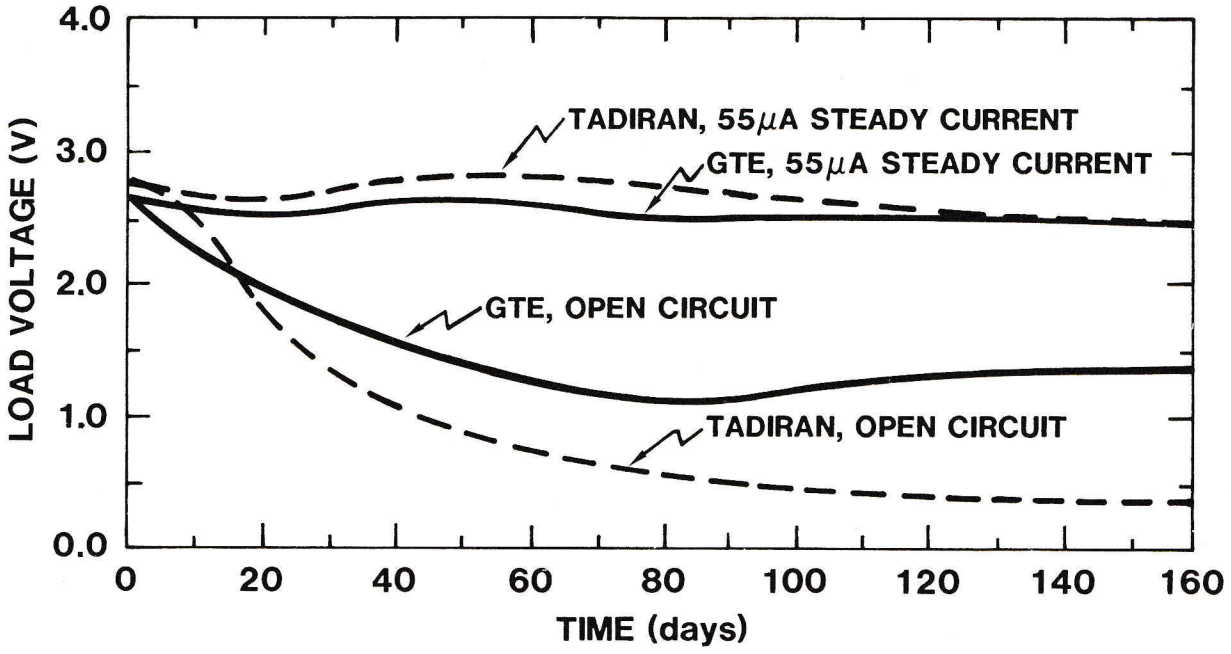

Figure 14. Minimum voltage under a simulated pump pulse load for single lithium-thionyl chloride cells as a function of time at 25°C. Cells were maintained open circuit or with a resistive load throughout the experiment.

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